

PANCREAS ALERTS

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Gallstone pancreatitis in older patients: are we operating enough?

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The recommended therapy for mild gallstone pancreatitis is cholecystectomy on initial hospitalization. Using a 5% national Medicare sample (1996-2005), the authors evaluated adherence to current recommendations for gallstone pancreatitis (cholecystectomy rates on initial hospitalization and the use of endoscopic retrograde cholangiopancreatography (ERCP)/sphincterotomy). The authors evaluated predictors of cholecystectomy, gallstone-related readmissions, and 2-year mortality. Adherence to current guidelines was low. Only 57% of 8,452 Medicare beneficiaries presenting to an acute care hospital with a first episode of mild gallstone pancreatitis underwent cholecystectomy on initial hospitalization. Of the patients who did not undergo cholecystectomy, 55% were never evaluated by a surgeon. Likewise, only 28% of patients who did not undergo cholecystectomy had a sphincterotomy. The 2-year readmission rates were higher among patients who did not undergo cholecystectomy (44% vs. 4%; $P < 0.001$), and 33% of these patients required cholecystectomy after discharge. In the no cholecystectomy group, ERCP prevented readmissions (hazard ratio, 0.53; 95% confidence interval, 0.47-0.61) and when readmissions occurred they were less likely to be for gallstone pancreatitis in patients who had an ERCP (27.8% vs. 53.2%; $P < 0.001$). On multivariate analysis, patients who were older, black, admitted to a nonsurgical service, lived in certain US regions, and had specific comorbidities were less likely to undergo cholecystectomy. In conclusion, the adherence to current recommendations for the management of mild gallstone pancreatitis is low in older patients. These data suggest that more than 40% of patients who did not undergo cholecystectomy would have benefited from early definitive therapy. Implementation of policies to increase adherence to guidelines would prevent gallstone-related morbidity and mortality in older patients.

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Pathobiology of acute pancreatitis: focus on intracellular calcium and calmodulin.

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The exocrine pancreas synthesizes all the enzymes needed for intestinal breakdown of proteins, fats, and carbohydrates in our diet. Unfortunately, the proteases needed for the digestion of the meat we eat can, if inappropriately activated inside the acinar cells, also digest the pancreas itself as well as the surrounding tissues, which is what happens in the sometimes fatal human disease acute pancreatitis. The disease is currently untreatable, but significant progress has recently been made in understanding the fundamental processes initiating the pathological changes underlying pancreatic autodigestion. It is now clear that intracellular trypsin activation (a crucial step in pathogenesis) is due to excessive release of Ca^{2+} from intracellular stores, principally via two types of inositol trisphosphate receptor. The unexpected recent discovery of an intrinsic protective mechanism caused by intracellular calmodulin and, specifically, the finding that this protective effect can be boosted by a membrane-permeable Ca^{2+} -like peptide are promising.

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Alteration in inflammatory/apoptotic pathway and histone modifications by nordihydroguaiaretic acid prevents acute pancreatitis in swiss albino mice.

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Reactive oxygen radicals, pro-inflammatory mediators and cytokines have been implicated in caerulein induced acute pancreatitis. Nordihydroguaiaretic acid (NDGA), a plant lignin, has marked anti-inflammatory properties. The present study aimed to investigate the possible protective effect of NDGA against caerulein induced pancreatitis. Acute pancreatitis was induced by intraperitoneal administration of eight doses of caerulein in male swiss albino mice. NDGA was administered after 9 h of acute pancreatitis induction. Pancreatic damage and the protective effect of NDGA

were assessed by oxidative stress parameters and histopathology of pancreas. The mRNA expression of heat shock proteins (DNAJ C15 and HSPD1) was examined by real-time RT-PCR analysis. Expression of HSP 27, NF-kappaB, TNF-alpha, p-p38, Bcl-2, p-PP2A, procaspase-3, caspase-3 and histone modifications were examined by western blotting. NDGA attenuated the oxidative stress, led to increased plasma alpha-amylase and decreased IGF-1 in AP mice. It modulated the mRNA and protein levels of heat shock proteins and reduced the expression of NF-kappaB, TNF-alpha and p-p38. It increased the number of TUNEL positive apoptotic cells in the pancreas of AP mice. In addition, NDGA prevented the changes in modifications of histone H3 in acute pancreatitis. NDGA prevents the progression of acute pancreatitis by involving alteration of histone H3 modifications and modulating the expression of genes involved in inflammatory/apoptotic cascade, which may be responsible for decreased necrosis and increased apoptosis in this model of acute pancreatitis.

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Neurodegenerative properties of chronic pain: cognitive decline in patients with chronic pancreatitis.

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Chronic pain has been associated with impaired cognitive function. The authors examined cognitive performance in patients with severe chronic pancreatitis pain. They explored the following factors for their contribution to observed cognitive deficits: pain duration, comorbidity (depression, sleep disturbance), use of opioids, and premorbid alcohol abuse. The cognitive profiles of 16 patients with severe pain due to chronic pancreatitis were determined using an extensive neuropsychological test battery. Data from three cognitive domains (psychomotor performance, memory, executive functions) were compared to data from healthy controls matched for age, gender and education. Multivariate multilevel analysis of the data showed decreased test scores in patients with chronic pancreatitis pain in different cognitive domains. Psychomotor performance and executive functions showed the most prominent decline. Interestingly, pain duration appeared to be the strongest predictor for observed cognitive decline. Depressive symptoms, sleep disturbance, opioid use and history of alcohol abuse provided additional explanations for the observed cognitive decline in some of the tests, but to a lesser extent than pain duration. The negative effect of

pain duration on cognitive performance is compatible with the theory of neurodegenerative properties of chronic pain. Therefore, early and effective therapeutic interventions might reduce or prevent decline in cognitive performance, thereby improving outcomes and quality of life in these patients.

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Spinal cord stimulation for visceral pain from chronic pancreatitis.

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Spinal cord stimulation (SCS) may reduce pain scores and improve function in patients with various chronic abdominal pain syndromes including chronic pancreatitis. Here described is a large clinical experience in SCS for severe chronic pancreatitis. SCS was trialed in 30 patients with chronic pancreatitis. SCS trials lasted 7-14 days (median 9 days). SCS lead tips were mostly positioned at the T5 (n=10) or T6 (n=10) vertebral level. Twenty-four patients (80%) reported at least 50% pain relief on completion of the trial. Among these, pre-trial visual analog scale (VAS) pain scores averaged 8 ± 1.6 (standard deviation) and opioid use averaged 165 ± 120 mg morphine sulfate equivalents. During the trial, VAS pain scores decreased to 3.67 ± 2 cm ($P < 0.001$, Mann-Whitney rank sum test) and opioid use decreased to 105 ± 101 mg morphine equivalent a day. Six patients failed the trial; one was lost to follow-up; in three patients after the implantation, the system had to be removed due to infection or lead migration; and 20 were followed for the whole year. For 20 patients followed for the whole year, VAS pain scores remained low (3.6 ± 2 cm; $P < 0.001$) at one year, as did opioid use (48.6 ± 58 mg morphine equivalents). In conclusions, SCS may be a useful therapeutic option for patients with severe visceral pain from chronic pancreatitis. Prospective trial is warranted.

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Randomised clinical trial: pregabalin attenuates experimental visceral pain through sub-cortical mechanisms in patients with painful chronic pancreatitis.

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Pregabalin has a broad spectrum of analgesic and antihyperalgesic activity in both basic and clinical studies. However, its mechanisms and sites of action have yet to be determined in humans. The authors aimed to assess the antinociceptive effect of pregabalin on experimental gut pain in patients with visceral hyperalgesia due to chronic pancreatitis and to reveal putative changes in corresponding central pain processing as assessed by evoked brain potentials. Thirty-one patients were randomly assigned to receive increasing doses of pregabalin or placebo for three consecutive weeks. Perceptual thresholds to electrical stimulation of the sigmoid with recording of corresponding evoked brain potentials were obtained at baseline and study end. The brain source localisations reflecting direct neuronal activity were fitted by a five-dipole model projected to magnetic resonance imaging of the individuals' brains. As compared to placebo, pregabalin significantly increased the pain threshold to electrical gut stimulation from baseline ($P=0.02$). No differences in evoked brain potential characteristics were seen, neither after pregabalin nor placebo treatment (all $P>0.05$). In agreement with this, brain source locations remained stable during study treatment (all $P>0.05$). In conclusion, pregabalin was superior to placebo for attenuation of experimental visceral pain in chronic pancreatitis patients. The authors suggest its antinociceptive effects to be mediated primarily through sub-cortical mechanisms.

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Neoadjuvant therapy in pancreatic adenocarcinoma: a meta-analysis of phase II trials.

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Neoadjuvant treatment has proven beneficial for many gastrointestinal (GI) malignancies, but no phase III trials have been completed examining this approach in pancreatic cancer. This meta-analysis examines the best available phase II trials using neoadjuvant treatment for resectable and borderline/unresectable pancreatic adenocarcinoma. Phase II trials were identified using a MEDLINE search, and the Cochrane Central Register of Controlled Trials from 1960 to July 2010. Patients were divided into two groups: Patients with initially resectable tumors (group A), and patients with borderline/unresectable tumors (group B). Primary outcome measures were rate of resection and survival. Pooled proportions and 95% confidence intervals (CIs) were calculated using random-effects or fixed-effects models based on the heterogeneity of included studies. A total of 14 phase II clinical trials including 536 patients were analyzed. After treatment, resectability was 65.8% (95% CI, 55.4-75.6%)

compared with 31.6% in group B (95% CI, 14.0-52.5%). A partial response was observed in patients with borderline/unresectable tumors; 31.8% (95% CI, 24.2-39.8%) in group B and 9.5% (95% CI, 2.9-19.4%) in group A ($P=0.003$). Progressive disease was seen in 17.0% (95% CI, 11.9-22.7) of patients in group A versus 21.8% (95% CI, 10.1-36.5%) in group B ($P=0.006$). Median survival in resected patients was 23 months for group A and 22 months for group B. Neoadjuvant treatment seems to have some activity in patients with borderline/unresectable pancreatic adenocarcinoma. Nearly one third of tumors initially deemed marginal for operative intervention were able to be ultimately resected after treatment. Until more effective targeted chemotherapeutics are developed, the only group of patients with pancreatic cancer that may benefit from neoadjuvant treatment are those with locally advanced disease.

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Genetically engineered mouse models of pancreatic cancer: unravelling tumour biology and progressing translational oncology.

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Pancreatic ductal adenocarcinoma (PDAC) remains a devastating disease despite tremendous scientific efforts. Numerous trials have failed to improve the outcome on this deadliest of all major cancers. Potential causes include a still insufficient understanding of key features of this cancer and imperfect preclinical models for identification of active agents and mechanisms of therapeutic responses and resistance. Modern genetically engineered mouse models of PDAC faithfully recapitulate the genetic and biological evolution of human PDAC, thereby providing a potentially powerful tool for addressing tumour biological issues as well as strategies for early detection and assessment of responses to therapeutic interventions. Here, the authors will discuss opportunities and challenges in the application of genetically engineered mouse models for translational approaches in pancreatic cancer and provide a non-exhaustive list of examples with already existing or future clinical relevance.

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c-Met is a marker of pancreatic cancer stem cells and therapeutic target.

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Growth of many different tumor types requires a population of self-renewing, cancer stem cells (CSCs). c-Met is a marker of normal mouse pancreatic stem and progenitor cells; The authors investigated whether it is also a marker of human pancreatic CSCs that might be developed as a therapeutic target. The authors studied growth of primary human pancreatic adenocarcinoma in NOD SCID mice. The self-renewal capacity of pancreatic cancer cells that expressed high levels of c-Met (c-Met(high)) was assessed using *in vitro* sphere assays, and compared with those that were c-Met-negative or expressed low levels of c-Met. The tumorigenicity of c-Met(high) pancreatic cancer cells was evaluated in NOD SCID mice. c-Met(high) cells readily formed spheres, whereas c-Met-negative cells did not. Use of the c-Met inhibitor XL184 or c-Met knockdown with small hairpin RNAs significantly inhibited tumor sphere formation. c-Met(high) cells had increased tumorigenic potential in mice; those that expressed c-Met and CD44 (0.5-5% of the pancreatic cancer cells) had the capacity for self-renewal and the highest tumorigenic potential of all cell populations studied. In pancreatic tumors established in NOD SCID mice, c-Met inhibitors slowed tumor growth and reduced the population of CSC, when given alone or in combination with gemcitabine. Administration of XL184 for 2 weeks after cardiac injection of cancer cells prevented the development of metastases. In conclusion, c-Met is a new marker for pancreatic CSCs. It is required for growth and metastasis of pancreatic tumors in mice and is a therapeutic target for pancreatic cancer.

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Bombesin receptor subtype-3 (BRS-3) regulates glucose-stimulated insulin secretion in pancreatic islets across multiple species.

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Bombesin receptor subtype-3 (BRS-3) regulates energy homeostasis, and BRS-3 agonism is being explored as a possible therapy for obesity. The authors studied the role of BRS-3 in the regulation of glucose-stimulated insulin secretion (GSIS) and glucose homeostasis. They quantified BRS-3 mRNA in pancreatic islets from multiple species and examined the acute effects of Bag-1, a selective BRS-3 agonist, on GSIS in mouse, rat, and human islets, and on oral glucose tolerance in mice. BRS-3 is highly expressed in human,

mouse, rhesus, and dog (but not rat) pancreatic islets and in rodent insulinoma cell lines (INS-1 832/3 and MIN6). Silencing BRS-3 with small interfering RNA or pharmacological blockade with a BRS-3 antagonist, Bantag-1, reduced GSIS in 832/3 cells. In contrast, the BRS-3 agonist (Bag-1) increased GSIS in 832/3 and MIN6 cells. The augmentation of GSIS by Bag-1 was completely blocked by U73122, a phospholipase C inhibitor. Bag-1 also enhanced GSIS in islets isolated from wild-type, but not Brs3 knockout mice. *In vivo*, Bag-1 reduced glucose levels during oral glucose tolerance test in a BRS-3-dependent manner. BRS-3 agonists also increased GSIS in human islets. These results identify a potential role for BRS-3 in islet physiology, with agonism directly promoting GSIS. Thus, in addition to its potential role in the treatment of obesity, BRS-3 may also regulate blood glucose levels and have a role in the treatment of diabetes mellitus.

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Differential improvements in lipid profiles and Framingham recurrent risk score in patients with and without diabetes mellitus undergoing long-term cardiac rehabilitation.

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Differential improvements in lipid profiles and Framingham recurrent risk score in patients with and without diabetes mellitus undergoing long-term cardiac rehabilitation. The authors aimed to determine whether lipid profiles and recurrent coronary heart disease (CHD) risk could be modified in patients with and without diabetes mellitus undergoing long-term cardiac rehabilitation (CR). This was a retrospective analysis of patient case records in a community-based phase 4 CR program. Patients without diabetes (n=154; 89% men; mean±SD age, 59.6±8.5 years; body mass index (BMI), 27.0±3.5 kg/m²) and patients with diabetes (n=20; 81% men; mean age, 63.0±8.7 years; BMI, 28.7±3.3 kg/m²) who completed 15 months of CR. Exercise testing and training, risk profiling, and risk-factor education were evaluated. Cardiometabolic risk factors and 2- to 4-year Framingham recurrent CHD risk scores were assessed. At follow up, a significant main effect for time was evident for decreased body mass and waist circumference and improved low-density lipoprotein cholesterol (LDL-C) level and submaximal cardiorespiratory fitness (all P<0.05), showing the benefits of CR in both groups. However, a significant group-by-time interaction effect was evident for high-density lipoprotein cholesterol (HDL-C) level and total cholesterol (TC)/HDL-C ratio (both P<0.05). TC/HDL-C ratio improved (5.0±1.5 to 4.4±1.3) in patients without diabetes, but showed no improvement

in patients with diabetes (4.8 ± 1.6 vs. 4.9 ± 1.6). The authors showed that numerous anthropometric, submaximal fitness, and cardiometabolic risk variables (especially LDL-C level) improved significantly after

long-term CR. However, some aspects of cardiometabolic risk (measures incorporating TC and HDL-C) improved significantly in only the nondiabetic group.
